Renal involvement in a large cohort of Chinese patients with Castleman disease

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Abstract

Background. The association of kidney disease with Castleman disease (CD) is uncommon. To date, most studies have been based on single-case reports. Here, we describe renal involvement in CD in a large Chinese cohort.

Methods. Seventy-six CD patients were identified in one clinical center. Clinical and pathological characteristics of patients with renal involvement were described, which were also compared with cases identified through a systematic literature review.

Results. Nineteen patients (25%) exhibited renal involvement. Patients with multicentric clinical type (59 versus 0%) or plasma cell (PC)/mixed cellularity histological variant (61.5 versus 6%) were more likely to have renal involvement (P < 0.001). Proteinuria (with 7/19 reaching nephrotic range) and acute renal failure (12/19, 63%) were the main clinical presentations. Kidney biopsy revealed various glomerular diseases (10/11) and interstitial nephritis (1/11), while thrombotic microangiopathy-like lesions were the most common pathological characteristics (6/11, 55%). This contrasted significantly with the literature in which amyloidosis was the most reported. Renal outcomes responded well to chemotherapy. Nine (9/12, 75%) patients with acute renal failure recovered completely, one recovered partially. Overall, only three (3/19, 16%) patients progressed to end-stage kidney disease. Renal involvement did not influence survival rate (log-rank test, P = 0.73) in the follow-up.

Conclusions. CD with multicentric type and PC or mixed cellularity variant are often associated with renal complications. Thrombotic microangiopathy-like lesions are the most common pathological characteristics. Chemotherapy can reverse kidney damage in most cases.

Keywords: Castleman's disease; cohort study; kidney disease

Introduction

Castleman disease (CD), also known as giant lymph node hyperplasia or angiofollicular lymph node hyperplasia, is a rare lymphoproliferative disorder first described by Castleman et al. [1]. Clinically, there are two types of CD: unicentric Castleman disease (UCD) or multicentric Castleman disease (MCD). Histologically, CD consists of three variants: hyaline vascular (HV), plasma cell (PC) or mixed cellularity (Mix). The HV variant is seen in 90% of CD and is characterized by the proliferation of capillary vessels in germinal centers of lymphatic follicles. It is typically associated with the UCD type and often exhibits less clinical manifestations and a benign prognosis. The PC variant is characterized by hyperplastic follicles and an interfollicular region containing sheets of plasma cells and is often associated with the MCD type, presenting with systemic manifestations, such as fever, malaise, weight loss, fatigue, edema, anemia, hypergammaglobulinemia, organomegaly and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) [2–4].

CD is sometimes associated with various renal manifestations, such as hematuria, proteinuria or renal failure. Renal biopsy reveals various lesions most frequently presented as amyloidosis [5]. However, most of these data come from single-case reports. Recently, a larger case series of 19 participants throughout France reported renal pathological characteristics in CD patients, with small vessel lesions as the most common renal pathology [6]. Here, we describe the clinical and pathological characteristics of renal involvement and its prognosis in a large cohort of 76 Chinese patients with CD from a single center in North China.

Materials and methods

Patient selection

Peking University First Hospital represents a general hospital in North China with 1500 beds, with most patients coming from Beijing and
North China. We reviewed all CD patients through the electronic medical record system of Peking University First Hospital from 1977 to 2010.

As described elsewhere [7], the diagnosis of CD in 76 patients was ascertained through the clinical database of Peking University First Hospital and confirmed through the pathology database of the same hospital. The sections of lymph node biopsies were centralized and reviewed by the pathologists in the Department of Pathology. In all patients, CD pathological diagnosis was based on histopathological biopsy specimen characteristics from involved lymph nodes, tissues or organs. Clinical involvement was ascertained by physical examination, computed tomography scan or ultrasound examination. Clinical features and laboratory tests at diagnosis and during treatment were also collected. Clinical and pathological characteristics of these patients from 1977 to 2008 have been reported previously [7], and here, we primarily describe renal lesions in a much larger cohort.

Renal involvement was defined as presenting with at least one of the following: (i) hematuria (red blood cell > 3 per high-power field), (ii) proteinuria (urine protein >150 mg/day) or (iii) renal function insufficiency: (i) hematuria (red blood cell > 3 per high-power field), (ii) proteinuria (urine protein >150 mg/day) or (iii) renal function insufficiency (serum creatinine >133 μmol/L) in patients with CD. These data were confirmed by a second value obtained at least 1 week after the initial evaluation. Other definitions in this study included anemia defined as hemoglobin <110 g/L, thrombocytopenia as <100 × 10^9/L, elevated erythrocyte sedimentation rate (ESR) as >15 mm/h for male and >20 mm/h for female, hypoalbuminemia as plasma albumin <35 g/L, and elevated serum IgG as >16.85 g/L. The clinical and pathological characteristics of patients with renal involvement are described. Data are also compared with those of control subjects without renal involvement.

Patients were followed to July 2010. Data were collected through telephone, letters and patients’ return visits.

Renal pathology
Renal biopsy specimens were examined by direct immunofluorescence, light microscopy (LM) and electron microscopy (EM) techniques. Renal biopsy specimens were fixed in 4.5% buffered formaldehyde for LM, and part of the sample was fixed in 2.5% paraformaldehyde for EM. Consecutive serial 3-μm sections were used for histological staining. The following staining techniques were used: hematoxylin and eosin, periodic acid–Schiff, silver methenamine and Masson’s trichrome. EM was performed according to standard procedures. After being embedded in epon, ultrathin sections were mounted on metal grids and stained with uranyl acetate before being viewed in a transmission electron microscope (JEM-1230; JEOL, Tokyo, Japan). Amyloidosis was diagnosed with the aid of Congo red staining. The pathological diagnoses of renal biopsies were all reviewed and confirmed by two experienced pathologists.

Literature search
The clinical and pathological characteristics of these group patients were also compared with other reports identified through systematic literature review. Electronic searches were performed in Medline (1950 through December 2010) using relevant text words and medical subject headings that included all spellings of CD and kidney involvement (Supplemental File 1). The literature search was limited to English language. Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies.

Statistical analysis
Dichotomous and polychotomous data were compared using the chi-square or Fisher’s exact test. Continuous baseline data were compared using Student’s-t test or the Mann–Whitney U-test. The Kaplan–Meier method was used to analyze survival between CD patients with or without renal involvement. Statistical analysis was performed using the SPSS version 13.0 statistical analysis program (SPSS Inc., Chicago, IL). A P-value of <0.05 was considered statistically significant.

Results
Baseline clinical and pathological characteristics
A review of the electronic medical record system of Peking University First Hospital from 1977 to 2010 identified 76 Chinese patients with CD, with a median age of 35.5 (range: 12–67) years and a male/female ratio of 43/33. Forty-four patients (57.9%) were clinically classified with unicentric CD, and the remaining 32 cases (42.1%) were diagnosed with multicentric CD. Histologically, 50 (65.8%) were HV variant, 13 (17.1%) were PC variant (Figure 1A and B) and 13 (17.1%) were mixed cellularity variant. All patients who received (60 patients) HIV screening (serum anti-HIV) were negative. Among these, 19 patients (25%) had renal involvement and all had multicentric CD (Table 1).

In the 19 patients with renal lesions, 17 (89.5%) suffered from at least one of the following: fever, weight loss and/or fatigue. Eleven (57.9%) had ascites and/or pleural effusion, and four had concomitant pericardial effusion. Seven (36.8%) had splenomegaly and two had concomitant hepatomegaly. Two patients (10.5%) were diagnosed with POEMS syndrome. Two patients presented with hypothyroidism, and Sjogren’s syndrome and xeroma were diagnosed in one patient each. Compared to subjects without renal involvement, patients with renal involvement were considerably more prone to have systemic symptoms (94.7% versus 49.1%, \( \chi^2 = 12.3, P < 0.001 \)).

As illustrated in Table 2, patients with renal involvement were much older (45.9 ± 15.3 versus 33.1 ± 12.1 years, \( t_{14} = 3.7, P < 0.001 \)) and more likely to be male (94.7 versus 43.9%, \( \chi^2 = 15.0, P < 0.001 \)). With respect to histological types, patients with renal involvement were mostly plasma or mixed cellularity variant (16/19, 84.2%), whereas those without renal lesions were mainly HV variants (47/57; 82.5%, \( \chi^2 = 28.1, P < 0.001 \)).

Laboratory tests
Compared with those without renal involvement, patients with renal complications were more likely to present with anemia (63.2 versus 14.8%, \( \chi^2 = 16.5, P < 0.001 \)), thrombocytopenia (36.8 versus 7.8%, \( P = 0.007 \)), elevated ESR (89.5 versus 60%, \( \chi^2 = 4.7, P = 0.03 \)) and hypoalbuminemia (68.4 versus 23.1%, \( \chi^2 = 12.5, P < 0.001 \)) (Table 2).

In addition, serum gammaglobulin was tested in 30 patients including 17 patients with renal involvement and 13 without kidney lesions. Elevated serum IgG was found in seven patients (7/17, 41.2%) with renal involvement and four (4/13, 30.8%) without renal involvement, respectively.

Antinuclear antibodies were detected in 3 cases of the 16 tested, anti-GBM antibodies in 2 (Cases 6 and 15) of the 12 tested and elevated rheumatoid factor in 3 of the 11 tested. Antineutrophil cytoplasmatic antibody (ANCA) was tested in 15 cases and 2 (Cases 1 and 5) were positive as detected by indirect immunofluorescence. A direct Coombs test was performed in 13 cases and 7 were positive. Only one patient (Case 6) received an HHV8 test in the lymph node using polymerase chain reaction amplifications and it was negative.

Because all cases with renal involvement were MCD, we compared clinical and pathological features in MCD patients with or without renal lesions. Similarly, patients with renal involvement were more likely to be male (94.7 versus 35.8%, \( P = 0.01 \)) and exhibited hypoalbuminemia...
However, no difference was observed between the two groups regarding age (45.9 ± 15.3 versus 37.8 ± 11.1 years, \( t_{30} = 1.63, P = 0.11 \)), histopathological type (84.2 versus 69.2% for PC or mixed variants, \( P = 0.4 \)), anemia (63.2 versus 30.8%), elevated ESR (89.5 versus 66.7%) and thrombocytopenia (36.8 versus 15.4%) (\( P > 0.05 \)).

\( \chi^2 = 4.7, P = 0.03 \).

Renal manifestations

Fourteen (74%) of the 19 CD patients with renal involvement presented with hematuria, 18 (95%) had proteinuria (median = 1.65 g/day; range, 0.22–12.6) and 7 (37%) reached nephrotic range. Twelve (63%) had acute renal failure (serum creatinine: 140–1035 μmol/L), and three (Cases 4, 5 and 6) required emergency dialysis. One (Case 7) presented with chronic renal failure with gradually elevated serum creatinine and progressed to end-stage kidney disease (ESKD).

Eleven of the 19 patients received a renal biopsy examination. The pathological findings (Table 3) included ‘thrombotic microangiopathy (TMA)-like’ lesions in six cases (6/11, 55%), with features of endothelial swelling, subendothelial space widening with double contour or subendothelial accumulation of protein and debris (Figure 1C–F), and crescentic glomerulonephritis in two cases (Cases 6 and 7) (2/11, 18%) and minimal change disease and chronic tubulointerstitial nephritis in one case each. The remaining one case (Case 15) presented with the histological features of both crescentic glomerulonephritis and membranous nephropathy. Of the two anti-GBM autoantibody-positive patients both revealed pathological features of crescentic glomerulonephritis (Cases 6 and 15, Table 4). The two (Cases 1 and 5) ANCA-positive patients did not undergo renal biopsy and presented with acute renal failure. In addition, one patient presented with acute renal failure (Case 16), skin biopsy revealed amyloidosis through Congo red staining, but renal biopsy was not performed.

The literature search yielded 158 case reports, of which 64 cases of CD with kidney involvement were identified from 59 publications (Supplementary File 2). Among these 64 patients with kidney biopsy available, amyloidosis was the most commonly reported renal lesion (25/64, 39.1%), followed by membranoproliferative glomerulonephritis (10.9%) and thrombotic microangiopathy (7.8%). Other renal pathological findings included mesangial proliferative glomerulonephritis (7.8%), interstitial nephritis (6.3%), membranous nephropathy (4.7%), crescentic glomerulonephritis (3.1%), minimal change disease (1.6%), focal segmental glomerulosclerosis (1.6%) as well as other lesions (17.2%) (Table 4).

Clinical follow-up

The therapy for patients with renal involvement was heterogeneous (Table 1). Seventeen patients received chemotherapy with COP (cyclophosphamide, vincristine and corticosteroid), CHOP (cyclophosphamide, adriamycin, vincristine and corticosteroid), RCHOP (rituximab and CHOP) or VP (vincristine and corticosteroid) regimen or with corticosteroid and/or cyclophosphamide. The remaining two patients only received supportive therapy.

Two of the 19 patients with renal involvement were lost during follow-up. The mean follow-up of the remaining 17 patients was 32 months (range: 2–100 months). Nine (75.0%) of the 12 patients with acute renal failure were considered recovered with serum creatinine normalized, 1 partially recovered with renal function stable during follow-up and only 2 patients (16.7%) reached ESKD.

Fig. 1. Histology of lymph node biopsy with PC variant (A and B) and renal biopsy with TMA-like lesions (C–F). (A) Hematoxylin and eosin (HE) ×40 and (B) HE ×200: enlarged cortex of lymph node contained hyperplastic lymph follicles with widening of interfollicular space, which was rich in PCs (↑). (C) HE ×200 and (D) PAS+Masson, ×200: the glomeruli showed lobular pattern with mild proliferation and severe swelling of glomerular endothelial cells, the capillary lumina was narrowed or nearly occluded with red blood cells (thin arrow). GBM was thickened with segmental double-contour appearance (thick arrow). (E) ×5000 and (F) ×10 000: electron micrographs of renal biopsy from the same case demonstrated severe widening of subendothelial space with electron-lucent flabby material and cellular processes, and the capillary lumen (*) was almost occluded with swelling endothelial cells. Red blood cells and its fragments were distributed in the subendothelial space and in capillary lumen.
Table 1. Clinical and pathological characteristics of CD patients with renal involvement

<table>
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<tr>
<th>No</th>
<th>Age</th>
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<th>LN</th>
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<th>Thrombocytes (×10^9/L)</th>
<th>Albumin (g/L)</th>
<th>ESR (mm/1 h)</th>
<th>CRP (mg/L)</th>
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<th>Renal histology</th>
<th>Therapy</th>
<th>Follow-up (months)</th>
<th>Renal outcome</th>
<th>Patients outcome</th>
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<td>70</td>
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<tr>
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</tr>
<tr>
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</tr>
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<td>Corticosteroid, HD, PE</td>
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<td>Die</td>
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<td>158</td>
<td>119</td>
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<td>Crescentic glomerulonephritis</td>
<td>COP, CHOP, PD, VP</td>
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<td>Partial remission of renal function</td>
<td>Survive</td>
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<td>Mix</td>
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<td>12</td>
<td>11.3</td>
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<td>Die</td>
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<td>COP, thalidomide</td>
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*ARF, acute renal failure; CHOP, adriamycin and COP; COP, cyclophosphamide, vincristine and corticosteroid; CRF, chronic renal failure; H, hematuria; HD, hemodialysis; F, female; M, male; Mix, mixed cellularity variant; MN, membranous nephropathy; P, proteinuria; NS, nephrotic syndrome; PD, peritoneal dialysis; PE, plasma exchange; RCHOP, rituximab and CHOP; RPGN, rapid progressive glomerulonephritis; VP, vincristine and corticosteroid.
For the remaining five patients, one (Case 7) with chronic renal failure progressed to ESKD and renal function of the remaining four patients was normal during the entire follow-up.

Four (4/17, 23.5%) patients with renal involvement and nine (9/48, 18.8%) without renal involvement died during follow-up, and there was no significant difference for patient survival between the two groups (log-rank test, P = 0.73) (Figure 2).

### Discussion

In this study, we described the renal involvement in 76 Chinese patients with CD. Among these, 25% patients presented with renal manifestations, particularly in those with the clinically multicentric type (59%), PC or mixed cellularity histological variants (61.5%). Acute renal failure, which occurred in >60% of the patients, represented the most common renal involvement, whereas thrombotic microangiopathy-like lesions were the most common pathological characteristics. The renal outcomes in patients with the CD were relatively good after chemotherapy and most patients recovered from acute renal failure. Renal involvement did not influence patient survival in CD patients during the follow-up.

To the best of our knowledge, our study represents the largest CD cohort study reported to date. CD is a rare
lymphoproliferative disorder. To date, renal involvement and its role in the progression of CD have been poorly understood. Only a limited number of small studies have reported on this. Kojima et al. [8] reported that 6 of the 28 Japanese multicentric CD patients (21%) had renal lesions (nephritis or renal failure). In another study involving 15 multicentric CD patients, 54% had renal impairment [9]. Our large study suggests that renal involvement is a very common complication in Chinese patients, particularly in those with the multicentric type, a PC/mixed cellularity histological variant. Importantly, our study revealed that the renal outcomes were relatively good in those patients receiving aggressive chemotherapy and that renal involvement did not influence patient survival. These findings will be considerably helpful when making clinical decisions.

Most studies regarding renal involvement and kidney biopsy are based on case reports. A literature review of 64 cases revealed amyloidosis as the main pathological characteristic in kidney biopsy (39.1%; Table 4) as well as other glomerular or interstitial renal lesions. Our cohort study indicates that thrombotic microangiopathy-like lesions are the most common renal lesions. This difference may arise from the report bias in case reports. Recently, another study [6] collected data from 19 CD patients across France, for whom kidney biopsy results were available. This study suggested that small vessel lesions (with TMA or membranous proliferative glomerulonephritis) were the most common renal lesions (Table 4). Our study and the French study strongly support the view that small vessel lesions, and not amyloidosis, are the most common renal complications of CD. These patients primarily present with decreased renal function but respond well to chemotherapy. It has been reported that vascular endothelial cell-derived growth factor secreted by tumor cells in CD plays a role in thrombotic microangiopathy-like lesions, although its exact functional role remains controversial [6, 10–12]. Thus, disease remission with chemotherapy or surgery also reverses the kidney damage. However, there are also some major differences between the Chinese and French groups. First, Amyloid A amyloidosis is still a common lesion in the French group, while in the Chinese group, only 1 of the 19 patients with renal involvement proved to be amyloidosis by skin biopsy. Second, we reported crescentic glomerulonephritis 3 of the 11 patients with kidney biopsy. Crescentic glomerulonephritis was not reported in the French study group and also seldom reported in others [13, 14]. Importantly, 4 of the 12 patients with acute kidney injury were found ANCA or anti-GBM autoantibodies positive. ANCA-associated small vasculitis was previously reported in another Japanese CD patient [13]. The autoimmune phenomenon had been reported in CD and it predominantly occurred in the multicentric type. Polyclonal B-cell activation caused hypergammaglobulinemia and production of autoantibodies [15]. These findings suggested that autoantibodies produced from the Castleman tumor cell might mediate renal lesions. Anti-GBM autoantibodies or ANCA should be routinely considered in the patients with CD and acute kidney injuries.

The strength of this study is the large number of cases examined and the careful data collection for a rare disease. There are, however, some major limitations, including the singlecenter focus (selection bias), retrospective study, short follow-up and some lost patients.

In conclusion, in this study of a large cohort, we found that renal involvement was very common in CD, particularly in those patients with the clinically multicentric type, and PC or mixed cellularity histological variant. Patients primarily presented with decreased renal function and often with proteinuria. Kidney biopsy revealed

### Table 4. Comparison between patients in present study and those from previous reports

<table>
<thead>
<tr>
<th>Renal histology</th>
<th>CD with renal involvement in our cases*, n (%)</th>
<th>CD with renal involvement in previous reports, n (%)</th>
<th>CD with renal involvement in a French cohort, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloidosis</td>
<td>0 (0.0)</td>
<td>25 (39.1)</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td>Mesangial proliferative glomerulonephritis</td>
<td>0 (0.0)</td>
<td>5 (7.8)</td>
<td>0</td>
</tr>
<tr>
<td>Small vessel lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
<td>6 (54.5)</td>
<td>12 (18.8)</td>
<td>9 (47.4)</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>1 (9.1)</td>
<td>3 (4.7)</td>
<td>0</td>
</tr>
<tr>
<td>Minimal change disease</td>
<td>1 (9.1)</td>
<td>1 (1.6)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Crescentic glomerulonephritis</td>
<td>3 (27.3)</td>
<td>2 (3.1)</td>
<td>0</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>1 (9.1)</td>
<td>4 (6.3)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>0 (0.0)</td>
<td>1 (1.6)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Others</td>
<td>11 (10.9)</td>
<td>64 (71.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

*One case presented with both crescentic glomerulonephritis and membranous nephropathy.

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**Fig. 2.** Analysis of survival of patients with CD with and without renal involvement. There was no significant difference in survival rate between CD patients with and without renal involvement.
various glomerular lesions, whereas thrombotic microangiopathy-like lesions are the most common. Chemotherapy successfully induces reversal of kidney damage in most patients, and renal involvement does not appear to influence patient survival.

Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

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